REDACTED 2/2/98

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

D1316 B

Food and Drug Administration
Rockville MD 20857

CBER-98-013

WARNING LETTER

JAN 30 1998

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Carol M. Moore
Vice President, Worldwide Regulatory Affairs
Bayer Corporation
800 Dwight Way
Berkeley, California 94710

Dear Ms. Moore:

During an inspection of your facilities located at 8368 U.S. Highway West. Clayton, North Carolina, between August 18 and October 14, 1997, and 800 Dwight Way, Berkeley, California, between December 1 and 11, 1997, our inspectors identified the following violations of Section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and Title 21, Code of Federal Regulations (21 CFR), Parts 211 and 600-680:

Clayton Facility

1. Failure to conduct and/or fully document a thorough investigation of an unexplained discrepancy or the failure of a batch to meet its specifications or extend the investigation to other batches that may have been associated with the specific failure or discrepancy [21CFR 211.192]. For example:

   a. Investigations of product sterility failures at Clayton do not extend to other products or processes which could be effected by the failure. (b)(4)
   b. The investigation of media fill failure (P-603B), for line [ ] at Clayton, did not extend to other products manufactured since the previous successful media fill on October 1, 1996. In addition, the investigation did not include a review of any equipment cleaning and sanitization records for the filling environment. Furthermore, the investigation was closed prior to any identification or review or the microorganisms recovered from the sterile fill operator whose microbial counts exceeded the established limits.
   c. The process for rebulking lots which have failed finished specifications for qualitites other than pyrogens and sterility has resulted in lots which

fail in-house specifications for pyrogenicity. There is no investigation, conclusion, or follow up at Clayton to determine the cause of increased pyrogenicity.

2. Failure to establish or follow written procedures designed to prevent microbial contamination of drug products purporting to be sterile [21CFR 211.113(b)]. For example:

   a. The standard operating procedures (SOP) entitled [redacted] [redacted]" states that "The contaminant will be characterized and possible relationships determined"; however, the investigation for media fill failure P-603B did not correlate the organism recovered from the tray loading operator with the organism found in the media fill units. (b)(4)
   b. There is no written specification for the maximum number of personnel allowed into the aseptic filling rooms at one time during the filling operation. Therefore there is no assurance that the number of aseptic filling employees who participate in media fills meets or exceeds the maximum number of employees who are required for routine production.
   c. There is no requirement that the media fills are conducted by personnel performing the same tasks they would normally perform during routine filling process.

3. Failure to assure an adequate system for monitoring environmental conditions [21 CFR 211.42 (c)(10)(iv) in that smoke studies to demonstrate unidirectional air flow have not been conducted for filling lines [redacted] (b)(4)

4. Failure to assure an adequate system for cleaning and disinfecting aseptic processing areas and equipment [21 CFR 211.42 (c)(10)(v)] in that the effectiveness of the process used to clean and disinfect aseptic processing areas and equipment has not been established. In addition, the effectiveness of the agents used has not been established.

5. Failure to follow, establish, or maintain specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160]. For example:

   a. The action limit for the cold WFI system has not been defined.
   b. Three consecutive port samples for the cold Water For Injection (WFI) must exceed [redacted] ml before action is considered. (b)(4)
   c. Ports [redacted] and [redacted] on the cold WFI system exceeded alert levels of [redacted] [redacted] ml on numerous occasions; however, appropriate action was

not taken to address the recurrence of contamination.

d. Document CQAB 02-041C indicates that action levels for environmental monitoring of aseptic filling operators are based on averaging of microbial results on a particular day, rather than counts obtained at specific personnel sites.

e. Air velocity measurements, specified in the SOP entitled [redacted] for the HEPA units over product lines exceeded the acceptance criteria of [redacted] (b)(4)

6. Failure to establish, maintain, or follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100]. For example:

a. The Batch Production Record entitled [redacted] does not state specific directions or an appropriate method to load and unload cages or partially filled cages containing final glass containers of Fraction V products into the pasteurizing tanks.

b. The SOP entitled [redacted]' does not define the appropriate actions to be taken when a CQAB 01-050C (Clayton Viable Particulate/Surface and Air Excursion Investigation Report For Class [redacted] and Class Areas) is issued as a result of an exceeded alert limit in a Bio Class r Bio Class nvironment. (b)(4)

c. The effectiveness of the cleaning agents used to clean the Fraction V pasteurization tanks has not been established.

d. There were no samples of non-pasteurized filled containers of Albumin, lot 691S007, tested as specified in the document entitled [redacted] The purpose of this test is to monitor the presence of heat sensitive microorganisms that would be killed during pasteurization.

7. Failure of each person engaged in the manufacture, processing, packing, or holding of a drug product to have training and experience to enable that person to perform the assigned functions [21 CFR 211.25 (a)]. For example:

a. Employees do not take part in a media fill prior to participation in routine filling.

b. There is no assurance that appropriate personnel are trained prior to implementation of new or revised procedures.

8. Failure to have an adequate acceptance criteria for sampling and testing to assure that batches of drug products meet each appropriate specification [211.165(d)]. For example:

    a. The effectiveness of the process used for inspecting final containers of Fraction V products for defects and proteinaceous material has not been established.
    b. There is no limit established for the number of times that a lot of final containers can be reinspected for the purpose of removing units containing proteinaceous material.

9. Failure to clean, maintain, and sanitize equipment at appropriate intervals to prevent malfunction or contamination that would alter safety, identity, strength, quality, or purity of the drug product and to establish or maintain written procedures for cleaning and maintenance of equipment [21 CFR 211.67]. For example:

    a. The effectiveness of the process for cleaning the Fraction V pasteurization tanks has not been established.
    b. The effectiveness of the process used to clean and remove cleaning agent residues from the fractionation kettles, bulk tanks, and centrifuge bowls has not been established.

(b)(4)

10. Failure to ensure that drug product containers and closures are clean and processed to remove pyrogenic properties [21CFR 211.94 (c)] in that the effectiveness of the [—] processor to depyrogenate the stoppers has not been established. The [~~] processor is used to clean and leech stoppers at Clayton.

11. Failure to assure that input and output from a computer has been checked for accuracy [21 CFR 211.68(b)]. For example:

    a. The database of microbial sampling results is not maintained in a manner that facilitates complete and accurate review of the data in that the employees' initials are not entered consistently.
    b. The database of environmental testing isolate is not maintained in a manner that facilitates complete and accurate review of data in that the same organism is entered into the computer with different spellings.

<u>Berkeley Facility</u>

1. Failure to clean, maintain, and sanitize equipment at appropriate intervals to prevent malfunction or contamination that would alter safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67(a)] in that the water bath used for viral inactivation and thawing of bulk Factor VIII is not sanitized. In addition, the effectiveness of the integrity of the container closure system used in viral inactivation

and in-process thawing has not been established. The water bath has had microbial counts of more than 3,000 colonies/ ml.

2. Failure to establish, maintain, or follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100]. For example:

   a. The SOP entitled '[redacted]' indicates that, in response to an adverse experience or technical report, other reports on the same lot or reports, of a similar nature, on different lots of the same product are reviewed. However, in practice, 10 lots manufactured before and 10 lots manufactured after the complainant lot are reviewed. (b)(4)
   b. The process used to establish the effectiveness of the lyophilization process for Thombate (AT-III) is inadequate in that only [redacted] vials from each lot are moisture-tested and [redacted] vials from each lot are assayed for solubility.

3. Failure to follow, establish, or maintain specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160] in that the current reference standards for all three products manufactured at the plant consist of old batches that have exceeded their manufacturing lot expiration dates.

4. Failure of the stability testing program to include reliable, meaningful, and specific test methods [21 CFR 211.166(a)(3)]. For example:

   a. Sterility of the stability samples has not been assured.
   b. The ability of the container closure system to maintain a vacuum is not assessed on stability samples.

It is significant to note that several of the same deviations or similar deviations, which represent serious violations of Current Good Manufacturing Practices, were observed and/or documented during the inspection at both facilities. These violations, noted below, are deficiencies which have significant impact to the overall operations at Bayer facilities.

Clayton and Berkeley Facility

1. Failure to establish or follow written procedures designed to prevent microbial contamination of drug products purporting to be sterile [21 CFR 211.113(b)]. For example:

a. The SOP at the Clayton facility entitled [redacted] does not:

(b)(4)

i. Designate who is responsible for conducting an investigation following a failure;
ii. Specify the requirements of the investigation;
iii. Designate who is responsible for reviewing the investigation prior to close out of the investigation; and
iv. Require documentation of the number of rejected units or the reason that the units were rejected.

b. There is no assurance that interventions are performed during media fills to simulate routine stoppage of equipment, entry into the aseptic curtained area and/or substitution of personnel during the operations at the Berkeley facility.

c. The sterilization validation program fails to demonstrate that equipment and components used in aseptic manufacturing are sterilized to a sterility assurance level of [-] in that a microbial challenge level of [-] spores is used.

d. The SOP at the Berkeley facility for media fills does not require the reason for rejected media fill units.

2. Failure to follow, establish, or maintain specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160]. For example:

a. An action level for microbial sampling of the Fraction V pasteurization tanks has not been established at the Clayton facility.

b. There are no specified limits on the microbial levels for the water bath used for viral inactivation and thawing in-process material at the Berkeley facility. Microbial counts from random sampling sites were more than 3,000 organisms per ml on November 24, 1997 and November 29, 1997, and more than 3,000 organisms on two occasions on November 18, 1997.

3. Failure to establish, maintain, or follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100]. For example:

(b)(4)

a. The SOP entitled '[redacted]' used at the Clayton facility, states that cold WFI hoses must be rinsed with hot WFI for no less than [-] seconds before use in sterile filling areas. However, the SOP entitled [redacted]

(b)(4)

[redacted]" states that cold WFI hoses must be flushed for minutes to mimic department practice. Furthermore, the Batch Record Control entitled "[redacted] " used in the filtering and dissolving departments does not contain specific instructions for flushing hoses: The SOP states that "Prior to use, rinse all hoses and related equipment with [redacted]

b. The SOP entitled "[redacted] used at the Berkeley facility states that WFI hoses are to be flushed not less than [redacted] with hot WFI prior to use. However, the SOP entitled "[redacted] instructs personnel not to flush WFI hoses.

4. Failure to maintain adequate written procedures describing the handling of all written and oral complaints regarding a drug product [21 CFR 211.198] in that the system for investigating complaints at both the Clayton and Berkeley facility is not complete and does not provide for an effective investigation. For example:

   a. Investigation requests sent to Clayton fail to include the contaminating organism.
   b. Investigation reports either sent to Berkeley or initiated by Berkeley do not include the details of all nonconforming materials reports, which address process deviations.

Written responses dated, October 31, November 7, November 26, December 5, December 12, and December 19, 1997, which address the inspectional observations on the Form FDA-483 issued at the close of the inspection at the Clayton facility are currently under review. In addition, we acknowledge receipt of your written response dated, January 20, 1998, which addresses the inspectional observations on the Form FDA-483 issued at the close of the inspection at the Berkeley facility. You will receive our assessment of all responses upon completion of our review. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate.

We acknowledge receipt of your document entitled "Bayer Master Plan for Conceptual and Systemic Improvements for Assurance of cGMP Compliance," dated, December 10, 1997, which includes time frames for process validation including rework methods. You will receive our evaluation of the Master Plan upon completion of our review. However, at this time we have one comment regarding the start time for the validation studies. The Master Plan indicates that validation studies will be initiated during the third quarter of 1998. This appears to be an excessive period of time to determine whether products are being manufactured consistently. It is our view that some level of review (e.g., defining critical process parameters and then retrospectively reviewing available data) may be appropriate to provide an initial assessment on the process until prospective or concurrent validation is completed.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deviations. We note that similar observations were made by our inspectors during previous inspections at the Clayton facility, the Berkeley facility, and other Bayer facilities. As management, it is your responsibility to assure that deviations corrected in one product system or area are also corrected in other product systems or areas of this facility as well as all facilities under your control to assure overall compliance with the provisions of the Federal Food, Drug and Cosmetic Act and all applicable regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes seizure and/or injunction, license suspension and/or revocation.

You should notify this office in writing, within 15 working days of receipt of this letter, of specific steps you have taken or will take to correct or prevent these deviations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to the following address: U.S. Food and Drug Administration; Center for Biologics Evaluation and Research; HFM-600; 1401 Rockville Pike, Suite 200N; Rockville, MD 20852-1448.

Sincerely,

Gerald Vince
Director, Office of Regional Operations

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